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Ocular Perfusion Pressure and the Incidence of Glaucoma: Real Effect or Artifact?: The Rotterdam Study

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PURPOSE. To determine the association between the ocular perfusion pressure (OPP; essentially the difference between the blood pressure and the intraocular pressure [IOP]) and incident open-angle glaucoma (OAG).

METHODS. A subset of 3882 participants of the population-based Rotterdam Study for whom data from ophthalmic examinations at baseline and follow-up and blood pressure measurements at baseline were available, and who did not have OAG at baseline, were included. Associations between the mean, systolic and diastolic OPP, and incident OAG were assessed using Cox regression models adjusted for age and sex, with and without adjustment for IOP.

RESULTS. During a mean follow-up of 9.8 years, 103 participants (2.7%) developed OAG. The association between the mean OPP and incident OAG was not significant (hazard ratio 0.995 per mm Hg increase in mean OPP; 95% confidence interval 0.971–1.019) when adjusted for IOP, but became significant if not adjusted for IOP (0.968; 0.945–0.992). The systolic and diastolic OPP showed a pattern similar to that of the mean OPP, though less significant.

CONCLUSIONS. The OPP appears to be associated with incident OAG but this association seems to be due to the fact that the IOP, a strong risk factor for OAG, is part of the OPP, rather than that OPP is an independent OAG risk factor itself. (*Invest Ophthalmol Vis Sci.* 2011;52:6875–6881) DOI:10.1167/iovs.11-7376

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Open-angle glaucoma (OAG) is a neurodegenerative disease that causes progressive damage to the optic nerve head and leads to visual field loss. Some of the risk factors for OAG have been identified; the most obvious risk factor is an increased intraocular pressure (IOP).^{1–3} It has been proposed that vascular components are also involved in the pathophysiology of OAG.^{4–10} One of the first studies showing a possible link between (systemic) blood pressure and OAG was done in 1911 in Germany.¹¹ Thereafter, many researchers studied the relationships between blood pressure and IOP and blood pressure and OAG. Blood pressure appears to be associated with the IOP; no unambiguous effect of blood pressure on OAG has been found thus far.^{12–21}

Blood pressure may affect the perfusion of the optic nerve head by influencing the perfusion pressure and also, especially in longstanding hypertension, by influencing the vessel diameter.²² The actual perfusion of the optic nerve head can be measured but these measurements are difficult to perform reliably, especially on a large scale.²³ For that reason, in epidemiologic studies, a proxy of the perfusion pressure is used rather than a measurement of the actual perfusion of the optic nerve head. In most tissues, the perfusion pressure equals essentially the difference between the arterial and venous blood pressure. In the eye, the actual mean ocular perfusion pressure (mean OPP; MOPP) is commonly estimated by the difference between the arterial blood pressure and the IOP (defined more precisely in the Methods section).^{5,24}

The relationship between the arterial blood pressure and OAG is complicated. As explained above, blood pressure is part of the MOPP, and a higher MOPP is presumed to decrease the risk of OAG. On the contrary, an increased blood pressure may reduce the vessel diameter and this might increase the risk of OAG. It becomes even more complicated when the IOP is taken into account as well. Because blood pressure is positively associated with IOP, systemic hypertension indirectly increases the risk of OAG. IOP is presumed to have a direct mechanical effect on the axons of the ganglion cells, but is also part of the MOPP—a higher IOP implies a lower MOPP. This implies that MOPP could pop up as a risk factor for OAG solely because IOP is part of it, and this might explain the contradicting results regarding the relationship between MOPP and OAG^{25–28}; some studies adjusted their analyses for IOP,^{16,19,29} whereas others did not.^{13,17,18,30}

The aim of this study was to clarify the intertwined relationships between blood pressure, MOPP and IOP, and OAG. Simply incorporating blood pressure, MOPP and IOP as three independent variables in a single model with OAG as the dependent variable is not informative. This is because, apart from being mutual confounding factors, the variables may be correlated too strongly (blood pressure and MOPP; IOP and MOPP) and may form a causal pathway (for example, IOP constitutes a causal pathway between blood pressure and OAG). For that reason, we first analyzed the association between MOPP and OAG with adjustment for IOP. Next, we

repeated the analysis without adjustment for IOP. We further explored the role of the IOP in the MOPP by replacing the blood pressure value in the MOPP of each participant by a randomly allocated blood pressure value of another participant and comparing the associations between MOPP and OAG before and after this replacement. Other factors that might be related to perfusion were also explored. Earlier studies reported a decreasing prevalence of OAG with an increasing diastolic OPP (DOPP).^{13,18} Therefore, we also assessed the relationships between systolic OPP (SOPP) and OAG and DOPP and OAG. Finally, we analyzed the association between blood pressure and IOP.

METHODS

Participants

The present study was performed within the Rotterdam Study, a prospective population-based cohort study of residents aged 55 years and older living in Ommoord, a district of Rotterdam, The Netherlands. The rationale and study design have been described elsewhere.^{31,32} All measurements were conducted after the Medical Ethics Committee of the Erasmus University had approved the study protocol and all participants had given a written informed consent in accordance with the Declaration of Helsinki. Baseline examination took place between 1991 and 1993; follow-up examinations for OAG were performed from 1997 to 1999 and from 2002 to 2006. The present study included only participants who completed at least one follow-up examination, had no OAG at baseline, and who had valid data on OAG, IOP, and blood pressure.

Ophthalmic Examination and Incident Open-Angle Glaucoma

The ophthalmic examinations at baseline and follow-up included a medical history, autorefractometry (Topcon RM-A2000; Tokyo Optical Co., Tokyo, Japan), keratometry (Topcon OM-4 Ophthalmometer; Tokyo Optical Co.), measurement of the best corrected visual acuity with Early Treatment Diabetic Retinopathy Study (ETDRS) optotypes, Goldmann applanation tonometry (Haag-Streit AG, Bern, Switzerland; see below), fundus photography of the posterior pole (Topcon TRC-50VT, Tokyo Optical Co., Tokyo, Japan), simultaneous stereoscopic fundus photography of the optic nerve head (Topcon ImageNet System, Topcon TRC-SS2, Tokyo Optical Co.), imaging of the optic nerve head (Heidelberg Retina Tomograph; Heidelberg Engineering, Dossenheim, Germany), and visual field testing (Humphrey Field Analyzer II 740 [HFA]; Carl Zeiss, Oberkochen, Germany).

The IOP was measured at baseline and at every follow-up round with Goldmann applanation tonometry after applying oxybuprocaine 0.4% eye drops and fluorescein from a paper strip. Three measurements were taken on each eye and the median value of these three measurements was recorded.³³ In the analysis we used the highest median IOP of both eyes.

The visual field of each eye was screened using a 52-point threshold-related supra-threshold test that covered the central field with a radius of 24°. Visual field loss was defined as nonresponse to a light stimulus of 6 dB above a threshold-related estimate of the hill of vision in at least three contiguous test points, or four including the blind spot. In participants with reproducible abnormalities on supra-threshold testing, Goldmann perimetry (Haag-Streit AG; baseline and first follow-up)³⁴ or full-threshold visual field 24 to 2 testing (second follow-up)³⁶ was performed on both eyes. The classification process of the perimetry test results have been described before.^{34,36} In short, visual field loss was considered to be glaucomatous visual field loss only if reproducible and after excluding all other possible causes.

Participants were considered to have incident OAG if neither eye had glaucomatous visual field loss at baseline and at least one eye showed glaucomatous visual field loss at follow-up.³⁶ Cases with a history or signs of angle closure (gonioscopy was performed in all identified cases) or secondary glaucoma were excluded.

Blood Pressure and Ocular Perfusion Pressure

Blood pressure was measured at baseline after the participant had been seated for at least 5 minutes. Systolic blood pressure (SBP; first Korotkoff phase) and diastolic blood pressure (DBP; fifth Korotkoff phase) were measured twice on the right arm using a random-zero sphygmomanometer with a 14 × 38 cm cuff. Afterward, we calculated the mean of the two SBP values and of the two DBP values.³⁷ The mean arterial blood pressure (MABP) was calculated according to $MABP = DBP + (SBP - DBP)/3$, where $SBP - DBP$ is the pulse pressure.³⁸ The MOPP was calculated according to $MOPP = \frac{2}{3}MABP - IOP$.³⁸ The SOPP and DOPP were calculated by subtracting the IOP from the SBP and DBP, respectively.

Potential Confounders

Other factors that might be related to perfusion are, following the Hagen-Poiseuille law, factors that influence the blood rheology (viscosity) or the vessel diameter (the diameter has a much a larger influence than vessel length and is more subject to change). The hematocrit is the major determinant of viscosity in the general population.⁷ Apart from blood pressure and hypertension, the vessel diameter may be influenced by smoking, diabetes mellitus, and serum cholesterol. For smoking and diabetes, trained research assistants asked participants about their smoking habits and if they had diabetes. Smoking was analyzed using nominal categories: never, former, and current smokers. Hematocrit and cholesterol levels were derived from blood samples taken at the research center. Serum cholesterol was quantified as the ratio of the high-density lipoprotein-bound cholesterol (HDL-C) and total cholesterol levels (HDL-C/cholesterol ratio). Another potential confounder is the body mass index.^{39,40} Body mass index was calculated as body mass in kilograms divided by the square of the height in meters. All potential confounders were determined at baseline.

Statistical Analysis

Differences in baseline characteristics were analyzed with independent *t*-tests and χ^2 statistics. We used Cox proportional hazard regression to calculate hazard ratios (HR) with corresponding 95% confidence intervals (CI) to analyze whether subjects with a high MOPP had a lower risk of developing OAG. The model fits were evaluated with C-statistics. Follow-up duration was used as the time variable. For participants without incident OAG, the follow-up duration was counted from the baseline visit to the last visit with reliable perimetry. For incident OAG cases, the follow-up was counted until the first visit in which glaucomatous visual field loss was detected. The multivariate model was created by first entering all covariates in the model. In the final multivariate model we included MOPP, age, sex, and those covariates reaching a significance of $P = 0.05$ or less in the initial multivariate model—except for IOP-lowering treatment (see Discussion). This final model was built with and without adjustment for IOP.

MOPP and IOP together in a multivariate model might lead to multicollinearity issues, because the IOP is part of the MOPP. To assess whether multicollinearity played a role in our analysis of MOPP adjusted for IOP we calculated the Pearson correlation coefficient and the variance inflation factor (VIF).

As mentioned in the introduction section, MOPP could pop up as a risk factor for OAG solely because IOP is part of it. To assess whether the blood pressure has an additional contribution to the significance of MOPP as a risk factor for OAG, we further explored the role of the MOPP by recalculating the MOPP after replacing the blood pressure value of each participant by a randomly allocated blood pressure value of another participant (sampling without replacement). Next, we recalculated the HR of the association between MOPP—without adjustment for IOP—and OAG. This was repeated 30 times. The resulting 30 HRs were compared with that of the original model. The same approach was applied for SOPP and OAG and DOPP and OAG.

The relationships between SOPP and OAG and DOPP and OAG were further explored by stratifying both SBP and DBP into five categories each containing approximately 19 OAG cases. For each of

TABLE 1. Baseline Characteristics of the Study Population with and without Incident Open-Angle Glaucoma

	Incident Open-Angle Glaucoma (<i>n</i> = 103)	No Open-Angle Glaucoma (<i>n</i> = 3779)	<i>P</i>
Age, y	67.8 ± 7.0	65.2 ± 6.8	<0.001
Sex, <i>n</i> (%) female	51 (49.5)	2221 (58.8)	0.060
IOP, mm Hg	18.2 ± 4.7	16.0 ± 3.1	<0.001
Treatment for IOP, <i>n</i> (%)	16 (15.5)	85 (2.2)	<0.001
Hematocrit Level (×100)	42.1 ± 3.0	41.5 ± 3.2	0.089
Systolic blood pressure, mm Hg	136.9 ± 21.0	135.7 ± 20.7	0.587
Diastolic blood pressure, mm Hg	73.2 ± 12.7	73.6 ± 10.8	0.721
Antihypertensives, <i>n</i> (%)	28 (27.5)	976 (25.8)	0.715
Smoking, <i>n</i> (%)			0.526
Never	33 (32.0)	1256 (33.5)	
Former	52 (50.5)	1698 (45.3)	
Current	18 (17.5)	791 (21.1)	
Diabetes mellitus, <i>n</i> (%)	7 (6.8)	142 (3.8)	0.120
HDL-C/cholesterol ratio	0.21 ± 0.06	0.21 ± 0.06	0.695
Body mass index	25.7 ± 2.9	26.3 ± 3.5	0.075

Data are presented as mean ± standard deviation unless stated otherwise with univariate comparisons; 324 participants had missing data on one or more covariates.

the SBP percentiles, a Cox proportional hazard regression was performed with SOPP as independent variable, and for each of the DBP percentiles, this analysis was performed with DOPP as independent variable. This was done with and without adjustment for IOP.

The relationship between blood pressure and IOP at baseline was analyzed by performing multiple linear regression analyses with IOP as the dependent variable and blood pressure, age, sex, treatment for IOP, and treatment for hypertension as the independent variables. This model was run for three different blood pressure variables: MABP, SBP, and DBP.

A *P*-value of 0.05 or less was considered statistically significant. All statistical analyses were performed using statistical analysis software (SPSS version 15.0.0 for Windows; SPSS Inc., Chicago, IL; and R statistical package version 2.9.1 for Mac; <http://www.r-project.org>).

RESULTS

The ophthalmic part of the Rotterdam Study comprised 6806 participants, of which 3939 had no OAG at baseline and participated at least in one follow-up round. Of these, 57 participants were excluded because of missing data on blood pressure or IOP. From the remaining participants, 103 out of 3882 (2.7%) developed OAG during follow-up.

Table 1 summarizes the baseline characteristics of the study population according to incident OAG status. Compared with participants without OAG, participants who developed OAG during the study were significantly older (*P* < 0.001), had higher baseline IOP (*P* < 0.001), and were more often treated for IOP at baseline (*P* < 0.001). None of the potential confounders (hematocrit, blood pressure, usage of antihypertensive drugs, smoking, diabetes mellitus, HDL-C/cholesterol ratio, and body mass index) showed significant differences between participants without OAG and those who developed OAG during follow-up. Body mass index was the only potential confounder that was significant in the initial multivariate analysis. We did not incorporate this variable in the final models because its presence did not change either the effect estimates or the significances of the relevant variables (IOP, MOPP, SOPP, and DOPP).

Table 2 presents the final multivariate models for MOPP with and without adjustment for IOP. We could not find an association between MOPP and incident OAG if adjusted for IOP (HR: 0.995 per mm Hg increase in MOPP; 95% CI: 0.971–1.019), but the association became significant after we re-

moved IOP from the model (HR: 0.968; 95% CI: 0.945–0.992). The C-statistics of the models with and without adjustment for IOP were 0.70 and 0.67, respectively. The Pearson correlation coefficient of MOPP and IOP was −0.227 (*P* < 0.001). The resulting variance inflation factor of 1.054 suggests that multicollinearity had no significant effect.

The role of adjusting for IOP or not, and thus the contribution of IOP to MOPP, was further assessed with the resampling technique as described in the Methods section. Figure 1A shows the results. The HRs of the resampled MOPP data scattered around the HR of the original dataset (solid line in Fig. 1A), indicating that the significance of the MOPP in a model without adjustment for IOP is essentially due to the fact that the IOP is part of the MOPP. Next, we investigated whether this finding could be explained by the fact that both the SBP and the DBP were taken together in the formula for computing the MOPP variable. If only one of these variables would contribute significantly, the statistical noise added by the other variable could have masked the effect. Models with SOPP and DOPP instead of MOPP revealed, with adjustment for IOP, a HR of 0.998 (95% CI, 0.987–1.008) for SOPP and a HR of 0.997 (95% CI, 0.978–1.016) for DOPP. The same models without adjustment for IOP yielded a HR of 0.994 (95% CI, 0.984–1.005) for SOPP and a HR of 0.980 (95% CI, 0.961–0.999) for DOPP. Figures 1B and 1C show the corresponding results of the resampling technique applied to the SOPP (Fig. 1B) and DOPP (Fig. 1C) data, respectively. Again, there was no clear difference between the original HRs (solid lines in Fig. 1B and

TABLE 2. Multivariate Cox Proportional Hazard Model for Mean Ocular Perfusion Pressure and the Risk of Developing Open-Angle Glaucoma

	Hazard Ratio	95% Confidence Interval	<i>P</i>
With adjustment for IOP			
Age, y	1.074	1.043–1.105	<0.001
Sex, female	0.594	0.393–0.898	0.014
IOP, mm Hg	1.168	1.114–1.224	<0.001
MOPP, mm Hg	0.995	0.971–1.019	0.675
Without adjustment for IOP			
Age, y	1.080	1.050–1.112	<0.001
Sex, female	0.554	0.368–0.834	0.005
MOPP, mm Hg	0.968	0.945–0.992	0.010

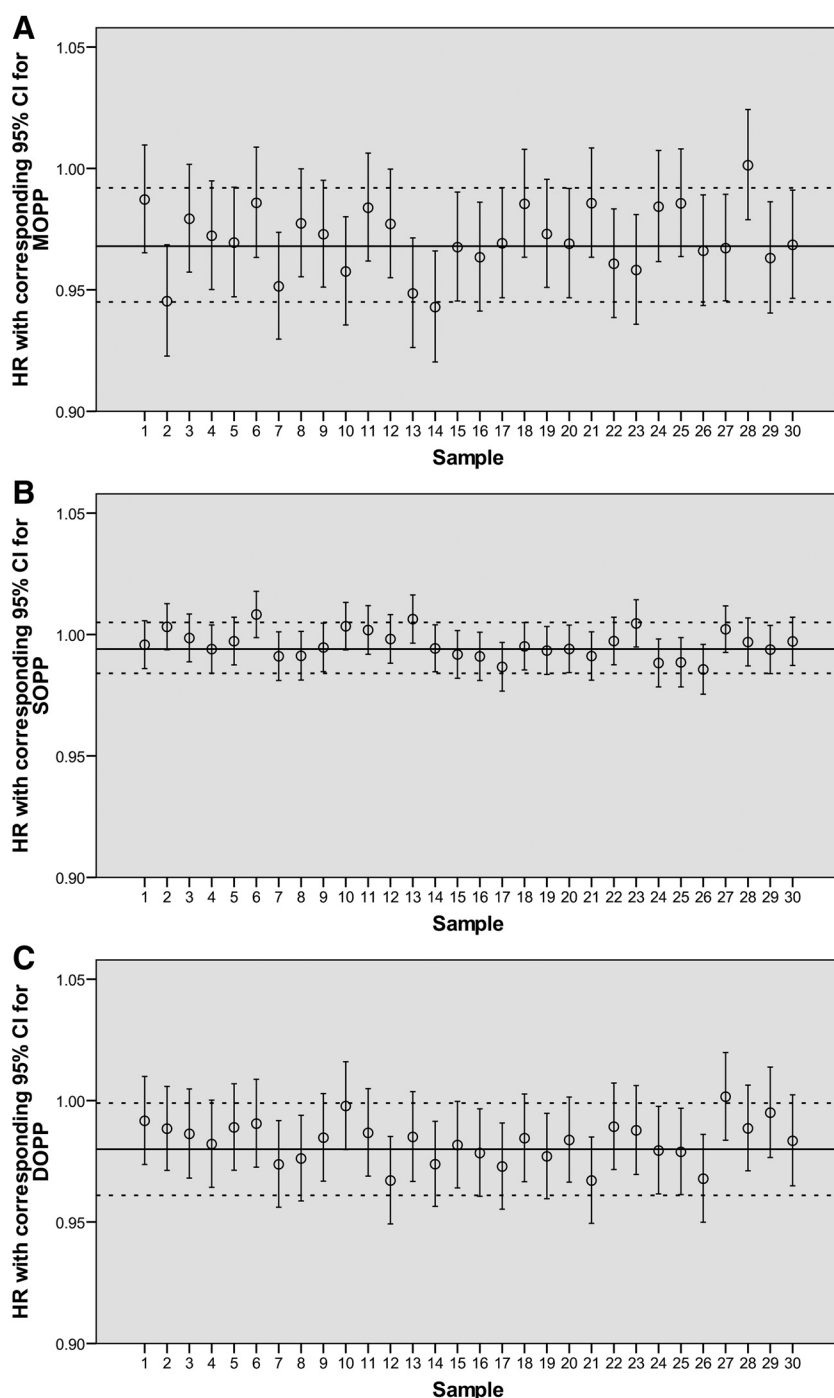


FIGURE 1. Hazard ratios and corresponding 95% CI for the resampled datasets of the associations between MOPP and open-angle glaucoma (**A**), SOPP and open-angle glaucoma (**B**), and DOPP and open-angle glaucoma (**C**). In the resampled datasets, the blood pressure value of each participant was replaced by a randomly allocated blood pressure value of another participant. *Solid line* represents the HR of the original dataset; *dotted lines* the corresponding 95% CI.

1C) and that of the resampled datasets, neither for SOPP nor for DOPP.

Figure 2 presents the relationships between SOPP and incident OAG and DOPP and incident OAG stratified for SBP and DBP, for models with and without adjustment for IOP. There were no clear associations with incident OAG, except for DOPP without adjustment for IOP, especially in subjects with lower DBP values (Fig. 2D).

Finally, we assessed the relationships between IOP and the blood pressure variables MABP, SBP, and DBP. IOP was strongly associated with all three variables ($P < 0.001$). The corresponding regression coefficients were 0.035, 0.025, and 0.029 mm Hg increase in IOP per mm Hg increase in MABP, SBP, and DBP, respectively. The percentages of variance in IOP

explained by the MABP, SBP, and DBP (R^2) were 2.0%, 2.5%, and 1.0%, respectively.

DISCUSSION

The MOPP appeared not to be an independent risk factor for OAG. Models without adjustment for IOP suggested a protective effect of a higher MOPP. This finding, however, could be explained by the fact that the IOP is part of the MOPP. A similar—albeit less obvious—protective effect was found for DOPP, but not for SOPP. This difference is most likely caused by the smaller SD of the DBP compared with that of the SBP (Table 1). A smaller SD in a blood pressure variable results in a

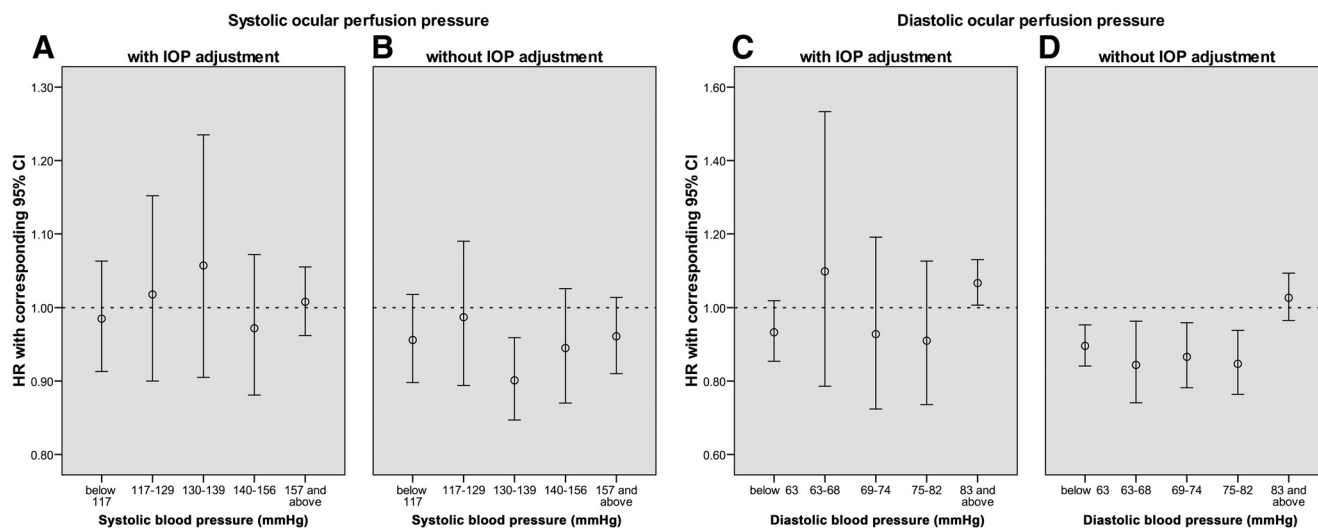


FIGURE 2. Hazard ratios and corresponding 95% CI of the associations between systolic ocular perfusion pressure and open-angle glaucoma, as a function of the systolic blood pressure (A, B), and between diastolic ocular perfusion pressure and open-angle glaucoma, as a function of the diastolic blood pressure. Analyses adjusted for age and sex with (A, C) and without (B, D) adjustment for the IOP.

larger contribution to the variability of the corresponding OPP variable explained by the IOP. This hypothesis is further supported by the finding that the highest DBP pentile had the highest SD and the least significant DOPP (Fig. 2D). The blood pressure variables were significantly associated with the IOP, but the variance of IOP explained by these variables was low, suggesting a minor importance in the pathophysiology of OAG (a 40 mm Hg change in SBP, for example, corresponded to a 1 mm Hg change in IOP).

Studies describing the possible association between MOPP and OAG used models with different covariates, making it difficult to compare results between these (epidemiologic) studies. Obviously, the most important covariate in this association is the IOP. Studies in which OPP was adjusted for IOP, The Barbados Eye Study,¹⁵ The Early Manifest Glaucoma Trial,²⁷ and The Blue Mountain Eye Study,¹⁹ could not find a significant association between MOPP and OAG. The Blue Mountains Eye Study found a modest increase in risk of OAG in participants with hypertension, especially in those who were poorly controlled. They also evaluated the potential relationship of OPP with OAG and OPP with ocular hypertension (the latter not adjusted for IOP). The relationship of OPP with OAG was significant for neither MOPP nor DOPP, but a marginal significance was found for SOPP with OAG ($P = 0.05$). For the relationship between OPP and ocular hypertension they found that only DOPP had a protective effect ($P = 0.0008$).¹⁹ Studies in which OPP was not adjusted for IOP, The Baltimore Eye Survey,¹⁸ The Egna-Neumarkt Study,¹⁷ Proyecto VER,³⁰ and previously our Rotterdam Study (but limited to persons receiving antihypertensive medications),¹³ found a reduced DOPP to be a risk factor for OAG. Hence, most studies reporting a low OPP as a risk factor for OAG were not adjusted for IOP—as was our approach in Table 2B, and most studies that failed to find an association between OPP and OAG were adjusted for IOP—as was our approach in Table 2A.⁴¹

Apart from possible limitations in the way MOPP is calculated from brachial artery measurements,⁴² the most obvious limitation of epidemiologic studies is the fact that measurements are performed only once and only during daytime. In this way, any circadian influence on blood pressure or IOP will be overlooked, as will be the influence of any other fluctuation. It has been suggested that fluctuations in IOP are more damaging to the optic disc than an increase in IOP.^{43–45} In addition, another study suggested that patients with progression of

OAG despite a normalized IOP suffer from insufficient autoregulation due to vascular dysregulation.⁴⁶ One study, evaluating the diurnal fluctuations (between 7 AM and 10 PM) of IOP and MOPP in participants with and without OAG, reported that patients with OAG do not have significant diurnal changes in IOP, but they observed significant fluctuations in the MOPP.³⁸ The range of diurnal fluctuations in IOP may be narrowed by IOP-lowering treatment and might be captured by analyzing large numbers of participants examined during the day. However, less is known about what happens during the night.⁴⁷ Patients suffering from unstable blood flow, due to vascular dysregulation, may be unable to compensate for physiologic fluctuations in IOP and blood pressure to maintain MOPP.⁴⁸ Besides, nocturnal dipping of blood pressure and circadian fluctuations in OPP are associated with the development and progression of OAG,⁴⁹ which is probably due to vascular dysregulation resulting in ischemia.^{28,50} Related to this, serum concentrations of endothelin-1 (vasoconstrictor) have been found to be slightly increased in patients with progressing glaucomatous visual field loss despite normal IOP.²⁸

Almost all participants in the Rotterdam Study are from European descent. Differences in properties of vascular factors (such as hypertension) across populations of different ethnicities have been described,⁵¹ and as a consequence findings on OPP might differ between populations.

The effect of IOP-lowering treatment was not taken into account in the main analyses of the present study—albeit significant in the univariate comparison (Table 1). Unlike the other covariates in Table 1, the IOP-lowering treatment is not in a potential physiological pathway affecting the risk of developing OAG. Moreover, this covariate is highly correlated with the IOP and the risk of developing OAG. It reflects the clinician's concern about the risk of glaucoma that may take into consideration for example the appearance of the optic disc and the family history. Nonetheless, if we would add the variable for IOP-lowering treatment to the analyses, the results did not alter significantly. Some antihypertensive drugs (e.g., calcium channel blockers) have been implicated in OAG.^{52,53} The current analyses evaluating the relationship between OPP and OAG were not adjusted for the usage of antihypertensive drugs (because the corresponding P -value was above 0.05 in the initial multivariate analysis). Re-entering either the usage of any antihypertensive drugs in the model or adding the usage of calcium channel blockers to the model did not change either

the effects estimates or the significances of the relevant variables (IOP, MOPP, SOPP, and DOPP; data not shown). The results on the relationship between MABP, SBP, and DBP and IOP were adjusted for the usage of antihypertensive drugs. The removal of this covariate did not change the findings. The body mass index was the only possible confounder that was significant in the initial multivariate model, but its presence in the model did not have any influence on either the IOP or the OPP variables (see Results section). Other factors such as smoking, diabetes mellitus, and cholesterol levels, are known to affect the vascular wall thickness through atherosclerosis. However, none of these factors was significant in the initial multivariate model. In an earlier study, we did not find an association between atherosclerosis and OAG.⁵⁴ In agreement with this, it has been suggested that it is not atherosclerosis but vascular dysregulation and insufficient autoregulation that leads to a low OPP (see also above).^{6,55}

In conclusion, we found no independent significant effect of OPP on the development of OAG. The current findings suggest that, in epidemiologic studies, the observed association between OPP and OAG is essentially due to the fact that the IOP is part of the OPP.

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